THE OXYGEN CONSUMPTION OF NEW-BORN AND ADULT MAMMALS. ITS DEPENDENCE ON THE OXYGEN TENSION IN THE INSPIRED AIR AND ON THE ENVIRONMENTAL TEMPERATURE

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Infants during birth and shortly afterwards are particularly liable to suffer from hypoxia, and much research has been directed to elucidating the effects of oxygen lack in the new-born. Evidence that moderate hypoxia (15% oxygen) causes a significant reduction in oxygen consumption in human infants was first produced by Cross, Tizard & Trythall (1955, 1958); it was later reported that lambs (Acheson, Dawes & Mott, 1957), and puppies and kittens (Moore, 1956a, b), respond in a similar fashion. It thus appeared that the new-born respond differently from adults, since it was generally accepted that the oxygen consumption of an adult mammal does not fall until death due to hypoxia is imminent (in the region of 6% oxygen). Then, in a review of the physiology of the new-born, McCance & Widdowson (1957) pointed out that adult *small* mammals behave in the same way as new-born animals, and not in the 'adult' manner. The situation was now confusing, since it was not clear whether it was *size* or *maturity* that determined the response to hypoxia. The present experiments were undertaken in order to make a direct comparison between new-born and adult animals of roughly the same size, and to obtain more information about the various types of response to hypoxia. A brief preliminary report of this work has been published (Hill, 1958).

METHODS

In order to investigate the effect on metabolism of hypoxia, immaturity, body size and environmental temperature, an apparatus had to be devised which would measure the oxygen consumption of a single unanaesthetized small mammal, breathing gas of any chosen composition between 21% and 5% oxygen in nitrogen, at various environmental temperatures. Good time resolution was essential, so apparatus that would give a continuous direct record was desirable.

Oxygen consumption may be measured by either open- or closed-circuit techniques, but for the present purpose open-circuit techniques were considered unsuitable. Their accuracy depends on

very small differences, and when dealing with animals of this small size only Haldane's gravimetric method is practicable. Even with this method, either time resolution or accuracy is bound to be poor when a single animal is used; and a continuous direct record cannot be obtained. A further disadvantage lies in the fact that any gas other than air must be supplied from a reservoir. Closed-circuit methods are more readily adapted to the problem in hand, since they permit much better time resolution, and easily lend themselves to graphic recording. In a closed circuit, if the CO_2 produced by the animal is absorbed, then the animal's oxygen consumption is indicated continuously by the amount of gas that must be added to keep the volume of the circuit constant.

A closed-circuit apparatus was adopted; its essential features are: (1) The oxygen content of the circuit gas is readily and predictably varied, as required, by removing and replacing oxygen, i.e. by altering the total volume of the circuit. (2) Once the chosen oxygen level has been attained an automatic device is then used to feed oxygen into the circuit at exactly the same rate as the animal consumes it. The volume of the circuit is held constant, and thus the composition of the circuit gas is kept constant while oxygen consumption measurements are made. (3) The amount of oxygen allowed into the circuit during each minute or half minute is recorded on a kymograph, measuring the animal's rate of oxygen consumption, $\Delta O_2/\Delta t$. (4) The need for a temperature-controlled room has been obviated by designing the apparatus in such a way that the total volume of the circuit is small; thus the error produced by changes in room temperature or barometric pressure during the course of an experiment is negligible compared with the oxygen consumption of even the smallest animal used. (5) The animal's environmental temperature can be rigidly controlled at any desired level. Full temperature equilibration between the circuit gas and the environment is rapidly achieved ($T\frac{1}{2} \approx 1$ min) after altering the environmental temperature. (6) It is essential for the proper interpretation of these experiments that the animal should be continuously under surveillance, since activity, degree of cyanosis and other effects must be assessed and taken into account: in this apparatus the animal is always clearly visible. (7) The animal's rectal temperature is indicated continuously.

The apparatus

This consists of two parts (see Fig. 1):

A. *A closed circuit* incorporates an animal chamber, a CO_2 absorber, a pump, a float recorder (Fig. 1, F_3), and devices for measuring and altering its oxygen content.

B. *A system for replacing and recording consumed oxygen* comprises: (i) Two float recorders, both containing oxygen; one (Fig. 1, F_1) of large capacity to record total oxygen consumption, the other (Fig. 1, F_2) of small capacity to record rate of oxygen consumption, i.e. to give a differentiated record, $\Delta O_2/\Delta t$; (ii) an electrical circuit to control and operate the system automatically. The three float recorders are described first, then the rest of the apparatus.

The circuit float (Fig. 1, F_3) has a capacity slightly greater than one-fifth of the total circuit volume in order to accommodate the volume changes produced by removing and replacing the oxygen in the circuit gas (the amount of nitrogen remaining unchanged). In this way the oxygen content of the circulating gas can be varied from 0 to 21 %; and the position of the float indicates the oxygen percentage. This float has a low inertia and rapid response even when counterbalanced; its capacity is 600 ml., yet it responds promptly to a change in volume of less than $\frac{1}{2}$ ml. The pressure inside it is always equal to ambient barometric pressure: this point is of some importance, see below.

The oxygen-differentiating float (Fig. 1, F_2) is of small capacity (*ca.* 12 ml.), and is weighted so that the pressure within it is maintained at 3 mm water above ambient barometric pressure. Thus gas can only pass from the differentiating float *into* the circuit, and not the other way. Between this float and the closed circuit is a valve to control the rate at which oxygen enters the circuit (electromagnetic valve Z in Figs. 1 and 2); this valve is actuated by a photo-electric device, which senses any tendency for the circuit float to fall (see electrical circuit II, Fig. 2). A vane (Fig. 1), fixed to the circuit float, cuts off light falling on the controlling photocell as the volume of gas enclosed in the circuit diminishes; this causes the valve to open, allowing oxygen to enter the circuit until the vane has been restored, when the valve again shuts.

The volume of gas enclosed in the circuit is maintained continuously constant to within 0·5 ml., and oxygen consumption rates as low as 2 ml./min can be satisfactorily recorded (for example, see Fig. 4). The photocell-and-light unit can be racked up and down and thus set in any position within the range of the circuit float; at each position of the photocell there will be a certain percentage of oxygen in the circuit gas.
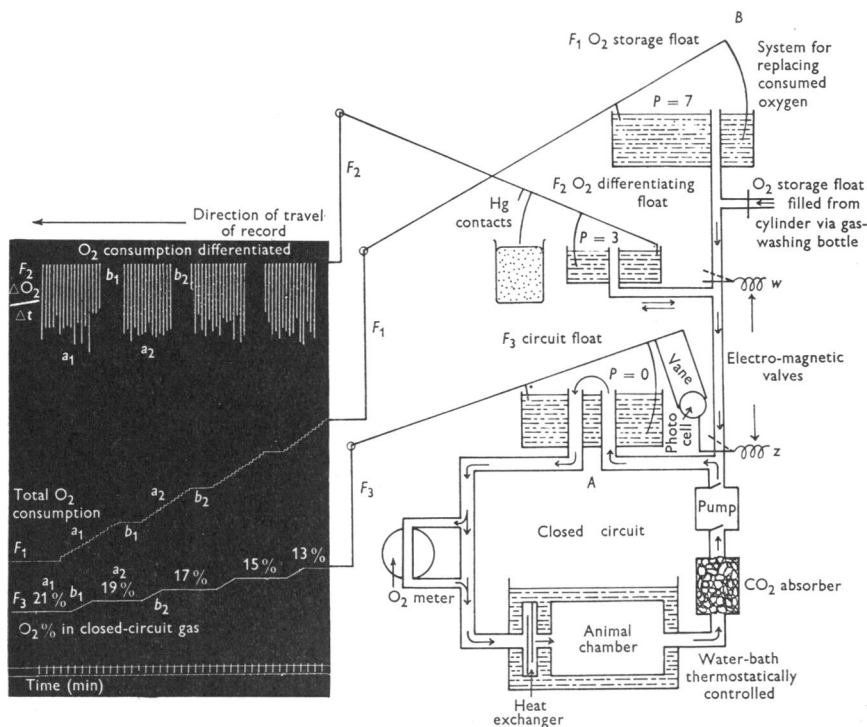

Fig. 1. Diagram of apparatus, together with specimen record. The record shows alternating periods during which the automatic oxygen replacement system either is in operation (labelled *a*) or is not (labelled *b*). When oxygen is not replaced, the diminution in circuit volume results from the removal of oxygen by the animal only, in this piece of record. Note that, to prevent them from fouling one another, the three frontal-writing levers are staggered so that they have a horizontal displacement relative to one another: for this reason the oxygen-differentiating float and the oxygen-storage float record with an apparent phase retardation of 4 min and 7 min respectively behind the circuit float. Pressure (mm H_2O) within each float is indicated in diagram in relation to atmospheric pressure, e.g. $P = 7$ indicates pressure 7 mm H_2O above atmospheric. Adult guinea-pig: environmental tempera-ture 30° C; $\Delta t = \frac{1}{2}$ min.

The filling of the oxygen-differentiating float is controlled by electrical circuit I shown in Fig. 2. This float is refilled regularly to a constant volume from the larger oxygen-storage float, via another electromagnetic valve (*W* in Figs. 1 and 2). The time interval is adjusted to suit the animal's rate of oxygen consumption: though, should the float become empty within the period of one time interval, it refills immediately; thus the oxygen percentage in the circuit gas can be rapidly increased merely by racking the photocell-and-light unit up to the appropriate setting (see Fig. 4).

To prevent both *W* and *Z* being open at the same time a high-speed relay in circuit I (*Y*, Fig. 2)

operates a change-over contact in circuit II, so that while current flows in I, the grid in II is short-circuited to earth; thus valve Z is held tightly shut whenever W is open.

The oxygen-storage float (Fig. 1, F_1) has a capacity of 600 ml.; the pressure within it is maintained at 7 mm water above ambient barometric pressure. The extra pressure is just sufficient to refill the differentiating float at a reasonable rate, but not big enough to cause a significant error in the volume measurement. This float is refilled from an oxygen cylinder as required, via a gas-washing bottle containing water; the oxygen it contains is in equilibrium with water vapour at room temperature.
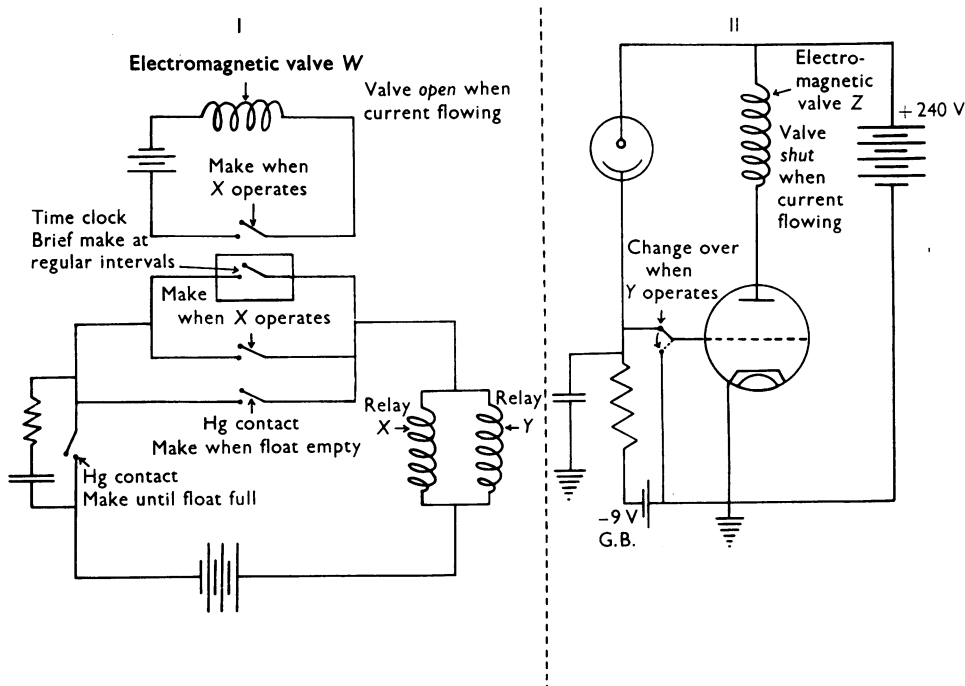

Fig. 2. Diagram of electrical circuit. Circuit I controls the filling of the oxygen-differentiating float. Circuit II controls the entry of oxygen into the closed circuit. The two mercury contacts and electromagnetic valve W in circuit I, and the photocell and electromagnetic valve Z in circuit II are also shown in Fig. 1, to indicate their positions in relation to the rest of the apparatus.

The oxygen-consumption record (see Fig. 1, section of record). When the oxygen-feed system is *not* in operation, the circuit float produces a trace which slopes upwards (the slope depends on the rate of disappearance of oxygen from the circuit gas), while the other two floats trace horizontal lines.

When the oxygen-replacement system *is* in operation, the circuit float traces a horizontal line— the position of this line indicates the oxygen percentage in the circuit gas. The oxygen-storage float produces a trace which slopes upwards, moving in a stepwise manner (each step represents one filling of the oxygen-differentiating float); the rate of rise gives an impression of the *average* rate of oxygen consumption. The differentiated record, however, shows up clearly small and transitory variations in oxygen consumption, which are more or less invisible in the storage-float trace (see Figs. 1 and 4). When the record has been measured up, though *total* oxygen consumption is obtained more easily and slightly more accurately from the storage-float trace, the

differentiated measurements are of greater value, because they are more accurate over short periods and readily lend themselves to statistical methods of analysis.

At the end of each experiment, the two oxygen floats are calibrated by removing known volumes of gas with a syringe; the calibration has remained constant for more than six months. For each record the sum of the volumes of oxygen discharged by the differentiating recorder over a period of about half an hour is compared with the volume of oxygen discharged from the storage tank over exactly the same period: the agreement between the two is almost always within 2%: however, if the difference is greater than this, the base line for the differentiating float is adjusted so that the two values correspond. All volumes of oxygen are finally calculated as dry gas at s.t.p.

The animal chamber is simply a Perspex cylinder of suitable size, so that the animal is unable to turn round; the ends are closed by rubber bungs through which pass glass tubes for circulation of gas. The animal's environmental temperature is rigidly controlled by immersing the animal chamber in a well-stirred water-bath, which can be thermostatically controlled at any desired temperature ($\pm 0.05°$ C). A heat exchanger (made from a piece of motor-car radiator), through which the circuit gas passes before entering the animal chamber, ensures that the temperature of the gas entering the chamber is always the same as that of the water-bath.

The CO_2 absorber is self-indicating soda-lime of fine mesh, firmly packed into a vertically mounted Pyrex tube. A gradual accumulation of CO_2 in the circuit gas during the course of the experiment would invalidate the results; with an animal in the circuit, gas leaving the CO_2 absorber can be bubbled through baryta water for many hours without producing more than a very faint trace of precipitate.

The circuit gas

Pump to circulate the circuit gas. The design and method of functioning of the whole apparatus impose certain rigid criteria for the pump, which, to be suitable, must have a very small capacity, and be absolutely leak-tight under operating conditions. Its rate of delivery must range from about 500 to 2500 ml./min, and the volume delivered must be largely independent of the back pressure to be overcome (which may amount to 1 ft. (30 cm) of water while oxygen is being absorbed). The flow of gas must be smooth and continuous, free from even momentary discontinuities which would disturb the accurate functioning of the oxygen-consumption recording system; also, the pump must not generate low-frequency vibrations, since these, by exciting resonance at certain positions of the circuit float, again would cause distortion of the oxygen-consumption record.

Various types of pump were tried. The circuit resistance is much too high for a centrifugal blower to be used. Roller and piston pumps are unsuitable because their delivery is not smooth and continuous; small motor-driven diaphragm pumps give rise to low-frequency vibrations. Eventually small aquarium pumps (driven at 100 c/s by a solenoid) were found to be satisfactory; though first they have to be made absolutely leak-tight by sealing with 'Araldite', an intake tube being added at the same time. These pumps then comply with the conditions listed above; since each pump delivers only about 800 ml./min either one, two or three are used in parallel, depending on the gas flow required.

To ensure that the animal does not re-breathe its own expired air, the rate of circulation of gas round the circuit is set so that it is equal to about four times the volume of gas contained in the animal chamber per minute; the geometry of the situation is then such that the gas advances down the animal chamber at a velocity of about 1·5 cm/sec. The animal is always placed in the chamber in a 'nose to wind' direction, so that CO_2-free gas is continuously provided at the head end.

Measurement of the oxygen content of the circuit gas. A rapid and reliable method for determining the oxygen content of the circuit gas is essential. At first small samples of about 0·5 ml. gas each were withdrawn from the circuit and analysed in a Scholander micro-gas-analysis apparatus. (I wish to thank Major Adam and his team at Hampstead for their kindness in teaching us this technique.) However, this method is time-consuming, and about 20 min elapses before the result is known; such delay tends to prolong experiments and to restrict their scope.

Fortunately, after a time, we were able to use a Cambridge Oxygen Measuring Unit (Magnetic Type, cat. no. 93631), which proved ideally suited to this purpose. (I am grateful to Professor H. Barcroft, St Thomas's Hospital Medical School, for the generous loan of this instrument.) Part of the circuit gas is diverted through the meter (Fig. 1). The instrument functioned with a reliable accuracy of $\pm 0.5\%$ over a long period. Incidentally its use provides a sensitive detector of leaks.

Lowering the oxygen content of the circuit gas. Incorporated into the circuit is an alternative route for the circuit gas, through a gas-washing bottle containing chromous chloride or anthraquinone, then through a tube packed with charcoal granules; this is normally kept sealed off from the rest of the circuit. To induce hypoxia, oxygen is removed rapidly from the circuit gas by passing it through the gas-washing bottle.

Standard of accuracy

Testing for leaks. All parts of the apparatus are joined together with glass or polyvinylchloride tubing (internal diam. ≈ 6 mm). A stringent leak test is always performed before each experiment is started, by running the kymograph with the circuit float both weighted and unweighted, and the oxygen floats full.

Consideration of possible sources of error. Change in volume in the closed circuit will accurately represent the oxygen consumption of the animal only if there are no other significant sources of volume change. The main possible causes of error arise from leaks, CO_2 accumulation, and changes in temperature; the first two have already been dealt with. So far as temperature is concerned, the apparatus has two well-defined regions. In the first the temperature is closely controlled; this consists of the animal tank and heat exchanger, which are immersed in the water-bath. In the second the temperature is not closely controlled; this comprises the rest of the apparatus, which is exposed to ambient temperature in a room without air-conditioning.

The animal tank and heat exchanger. The thermostatic control of the water-bath is so accurate that no detectable variations in circuit volume arise from this source while the water-bath is maintained at constant temperature. The volume change which occurs when the temperature is changed can be measured: it follows an exponential time course, with a half-time of about 1 min; its magnitude depends on the size of the animal chamber used, and the amount by which the temperature is changed. For practical purposes, the volume change is complete 3 min after the water-bath temperature has reached a new level.

The rest of the apparatus. The capacity of this part of the circuit has been kept to an absolute minimum. In effect, the volume of gas exposed to ambient temperature varies between 800 and 1200 ml., depending on the position of the circuit float. The room and circuit-gas temperatures are fairly stable; though both gradually rise during the course of the day, the rate of rise is never faster than $1° C$/hr, and usually much less than this. The maximum error which could be produced in this way is negligible compared with the oxygen consumption of even the smallest kitten. Changes in barometric pressure occurring during the course of an experiment do not give rise to a significant error.

Other possible sources of error. For about 10–15 min after the animal is first put into the chamber, and the apparatus set running, heat and water-vapour equilibration will be taking place; after that there will be no further volume change from this cause. Excess water is removed in a cooled tube.

It is observed that during an experiment the oxygen percentage in the circuit gas very gradually and steadily falls; this means that less oxygen is entering the circuit than the animal is actually consuming. The deficit (6–8 ml. O_2/hr) is too great to be accounted for solely by the rise in room temperature, and the effect must be due to contamination with a 'foreign' gas.

It is not due to a leak, because when the apparatus is running without the animal in the circuit the volume of the enclosed gas and the oxygen meter reading stay more or less constant. Such an effect would occur if the oxygen entering the circuit was slightly impure. The oxygen derived from a cylinder seems to contain something like 0.2% of inert gases (my estimation, using the Scholander technique). Because the amounts involved are so small it is impossible to demonstrate how much of the fall in oxygen percentage is accounted for in this way. In so far as this is the source

of the oxygen deficit, it will give rise to no error in the oxygen consumption measurements, because for say 10 ml. oxygen consumed, exactly 10 ml. gas will be replaced, and measured as oxygen consumed.

There is also the possibility that gases other than CO_2 are produced by the animal. Hydrogen and methane are generated in the intestines of herbivores during digestion (Krogh, 1916). Ruminants certainly produce considerable quantities of methane; however, the rate of production falls rapidly after feeding, becoming minimal 16–24 hr after the last meal (Brody, 1945, pp. 26–32, 323). Methane is difficult to estimate quantitatively, and I could find no recorded measurements of methane production by the guinea-pig. To minimize this error the guinea-pigs used for these experiments were starved for 24–48 hr, and their methane production must have been small.

Animal management

All the experiments were performed with unanaesthetized animals, either kittens or adult guinea-pigs.

Kittens were used from within an hour or so of birth up to 40 days of age; they were not starved before the experiment, and were returned to their mothers immediately afterwards. The experiments did not appear to harm them, and they throve and gained weight quite as well as their unused sibs. Usually the same kitten from a litter was used for a whole series of experiments. At birth a kitten weighs 80–120 g; by about 9 days of age it has doubled, and at 3 weeks trebled, its birth weight; the range of weight of all the kittens used was 80–550 g. To get consistent results it is essential that the animal should not become damp during the experiment, so the kitten's bladder was emptied before it was put into the chamber (by gently stroking the perineum with cotton-wool).

Guinea-pigs were deprived of food for 24–48 hr, and of water for 12 hr, before an experiment. They were housed as far as possible at a constant environmental temperature of 65° F (19° C). The range of weight of the guinea-pigs was 225–850 g.

Experimental procedure. The animal's rectal temperature was measured to within $\pm 0.025°$ C by means of a copper-constantan thermocouple, thinly sheathed in polyvinylchloride tubing. This was left *in situ* throughout the experiment. After weighing the animal the thermocouple, lubricated with xylocaine ointment, was inserted as far as possible (at least 4 cm beyond the anal margin in kittens, further in guinea-pigs) and secured in place with tape. The thermocouple is fine and flexible and its presence does not disturb the animal.

Though unsedated, the animals settled down quickly after being put into the apparatus, and generally remained quiet or slept through most of the experiments: the humming noise of the pumps, and the absence of other sensory stimuli may combine to produce a soporific effect. The occurrence of activity was always noted down, its intensity being specified in terms of an arbitrary five-point scale. Also, at intervals of 5–10 min throughout each experiment, the following readings were recorded: the animal's rectal temperature; the temperature of the water-bath, the room air and the circuit gas; and the oxygen-meter reading. At the same time any other observations relevant to the state of the animal were noted down also (e.g. whether cyanosed when hypoxic). A clock was set going at the same time as the oxygen-consumption recording was commenced, so that later the hand-written information could be accurately keyed to the record of oxygen consumption obtained automatically.

RESULTS

The effect of hypoxia in relation to maturity

The first question which has to be answered is whether it is only *new-born* animals that respond to hypoxia by reducing their oxygen consumption. This was investigated by comparing kittens aged 1–40 days with adult guinea-pigs of roughly the same size; oxygen consumption was measured while the animal

was breathing various percentages of oxygen ranging from 25 to 6 %. In these preliminary experiments the environmental temperature of the animals was not rigidly controlled: it varied, depending on the room temperature, from 20 to 27° C, though usually it lay between 21 and 24° C. This temperature range is not very great, and the temperature variations were similar for
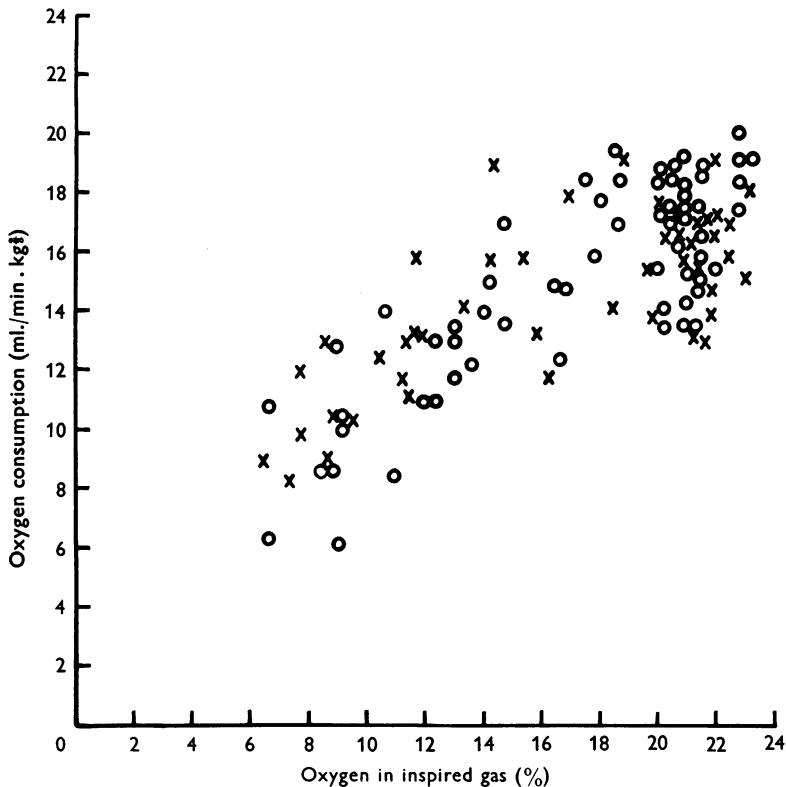

Fig. 3. The effect of hypoxia on the oxygen consumption of kittens aged 1–40 days (○), and adult guinea-pigs (×). The environmental temperature was not rigidly controlled but varied from 20 to 27° C according to the ambient temperature; however, the temperature variations were roughly similar for both species. Oxygen consumption is plotted in units which minimize the effect of variation in size between one animal and another; see text.

both species. Incidentally, none of the animals was ever observed to shiver at these environmental temperatures.

The results obtained are shown in Fig. 3, where oxygen consumption (ordinates) has been plotted against the oxygen percentage in the inspired gas (abscissae). Each point represents one animal's average oxygen consumption over a 10–20 min period.

Because kittens grow very rapidly after birth (p. 352), the animals actually varied considerably in size; the heaviest weighed about six times as much as

the lightest. Therefore oxygen consumption could not be plotted directly, i.e. in (ml./min) per animal: nor would plotting it in (ml./min) per kilogram have been satisfactory, since it is well known that larger animals have a lower oxygen consumption per kilogram than smaller ones, merely because of their size (see e.g. Brody, 1945, p. 354). The effect of size was minimized by plotting oxygen consumption in (ml./min) per kilogram$^{\frac{2}{3}}$: this procedure will be justified later (p. 355).

Though the scatter is rather large, Fig. 3 shows no obvious difference between kittens and adult guinea-pigs in their response to hypoxia: both showed decreased oxygen consumption more or less in proportion as the oxygen content of the inspired gas was reduced below about 15%. It was noted that in every case in which hypoxia produced a fall in oxygen consumption a fall in rectal temperature occurred also.

The inference is that reduction in oxygen consumption as a result of hypoxia is not a response specifically shown only by *new-born* animals. But the animals were chosen so that both new-born and adults were small, and of a roughly similar size, so the question arises whether this particular response to hypoxia is characteristic of mammals of small size, regardless of age. This is dealt with below (p. 365).

The effect of environmental temperature

It has been known for a long time that adult mammals increase their rate of metabolism when the environmental temperature is low; in general, the smaller the animal, the more sensitive it is to a small change in environmental temperature. Thus for a close analysis of the relation between oxygen consumption and hypoxia, the environmental temperature must be taken into account as a third and independent variable. Incidentally, its control should have the advantageous effect of reducing the scatter of the observations.

The effect of environmental temperature on the metabolism of adult guinea-pigs has been investigated by Herrington (1940), but no such study has been made on kittens. Therefore, the relation between oxygen consumption and environmental temperature in kittens breathing 21% oxygen had to be investigated in detail; a similar study in adult guinea-pigs was also made for comparison. To keep this paper reasonably short the experimental results of these investigations will have to be given in a later paper; this one will deal in detail only with the effect of hypoxia. However, to understand what follows, it will be necessary to accept in advance the following findings.

Kittens from within a few hours of birth were able to maintain a reasonable body temperature (in the region of 37·5–39° C) in the face of environmental temperatures down to 28° C. They did this by increasing their oxygen consumption above the basal level. Their neutral temperature zone (i.e. the range of environmental temperatures at which metabolism was minimal) was in

the region of 34–36° C (under the experimental conditions of this apparatus). In their ability to produce a metabolic response to cold they showed qualitatively the same reactions as an adult homoeotherm (e.g. guinea-pig). Both kittens and adult guinea-pigs were able to double their basal metabolic rate without shivering: and at the environmental temperatures used in these experiments, shivering was never observed. (For a preliminary report of these observations, see Hill (1958).)

The effect of size

In Fig. 3, where the oxygen consumption of kittens and adult guinea-pigs of various sizes had to be compared, oxygen consumption was plotted in (ml./min)/kg$^{2/3}$, in order to minimize the effect of size. This is effective only when metabolic rate is proportional to (body weight)$^{2/3}$. Metabolic rate has been variously reported as being proportional to:

(body weight)$^{2/3}$, the classical Surface Law (Sarrus & Rameaux, 1839);

actual skin area (e.g. DuBois & DuBois, 1915);

(body weight)$^{0.73}$ (Brody, 1945, p. 370);

(body weight)$^{3/4}$ (Kleiber, 1947).

It is not certain which of these expressions applies best to mature animals; and moreover, when *growing* animals are considered, there is evidence that none of these expressions may be found to apply (see e.g. Brody, 1945, pp. 404–450). A discussion of the reasons for the disagreement cannot be entered into here. Under the circumstances the only satisfactory procedure was to determine experimentally how metabolism did vary with size in the particular animals under consideration, and this has been done. Again, the details of the investigation will have to be given in a later paper, but the essential finding that must be briefly reported here is that the basal metabolic rate of both kittens and adult guinea-pigs of various sizes is rather precisely related to (body weight)$^{2/3}$; and for both has a value in the region of 10 ml./min. kg$^{2/3}$. At environmental temperatures below a neutral value this relation no longer holds true: but this fact has not affected the decision to plot all comparative measurements of oxygen consumption 'per kg$^{2/3}$'; this remains the simplest and most reasonable thing to do, no matter what the environmental temperature is.

It is thus seen that a comparison of the effect of hypoxia on the oxygen consumption of kittens and adult guinea-pigs actually turns out to be very complicated. Oxygen consumption, which is the parameter measured, is certainly affected by the size of the animal, its thermal insulation and the environmental temperature to which it is exposed, as well as by the oxygen tension in the gas that it breathes; and detailed knowledge of the interrelation between *all* these variables is necessary in order to define accurately the relation between any two of them. In conjunction with these factors, the possible effect of

species and maturity has also to be considered. We can now return to the investigation of the effect of hypoxia.

The effect of hypoxia in relation to environmental temperature

Kittens

Below the neutral temperature. Figure 4 shows the kymographic record of an experiment performed at a controlled environmental temperature of 28° C, in
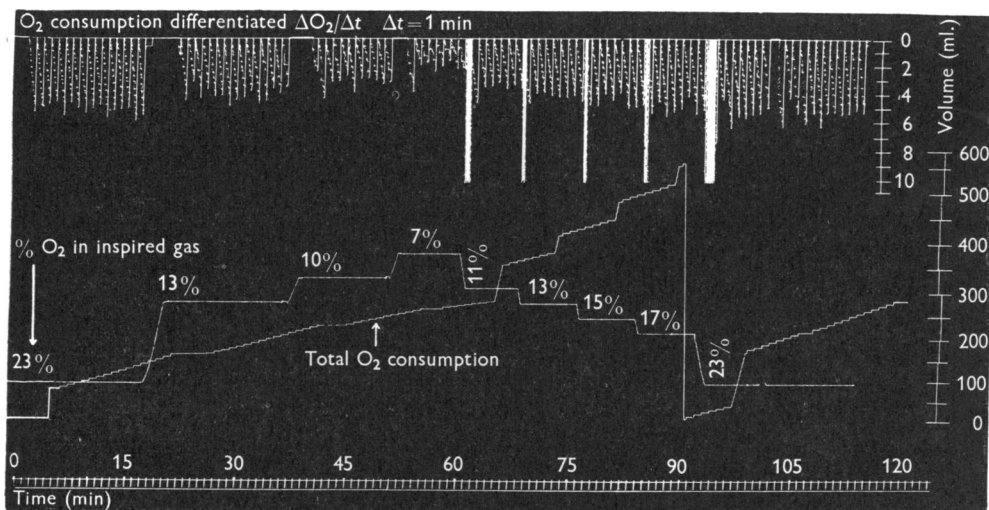

Fig. 4. Experimental record showing the effect of hypoxia on the oxygen consumption of a kitten, age 5 days, weight 145 g. Environmental temperature controlled at 28° C (below the neutral temperature). Oxygen was removed from the circuit gas with the aid of an oxygen absorber. It was replaced by racking the photocell-and-light unit up to the desired position, so that the oxygen-differentiating float repeatedly emptied into the circuit and refilled (shown by the heavy white lines), until the required amount of oxygen had been replaced, when automatic oxygen-consumption recording recommenced. Note that because the writing levers are staggered (see legend to Fig. 1), the oxygen-differentiating and storage floats apparently record 1 min and 5 min respectively behind the circuit float.

which the oxygen content of the gas breathed by a kitten was first lowered in stages, then restored in stages; oxygen consumption being measured at each oxygen level. The record shows a prompt and obvious decrease in oxygen consumption with each reduction in the oxygen level; the more severe the hypoxia, the greater the reduction in the oxygen consumption. The oxygen content of the circuit gas was restored in stages, and the record shows a stepwise increase in oxygen consumption. The environmental temperature, 28° C was below the neutral temperature for this animal, and this result is obviously similar to the results obtained in the preliminary experiments (see Fig. 3).

At the neutral temperature. Another experiment in which a kitten was sub-

jected to hypoxia at a controlled environmental temperature is shown in Fig. 5, but here the effect of a given degree of hypoxia (10 % oxygen) was compared at two different environmental temperatures, first at the neutral temperature (34° C), then at 26° C (below the critical temperature). Clearly, at the *neutral* temperature hypoxia of this degree did not produce a change in either the animal's oxygen consumption, or its rectal temperature. In contrast, when the animal's oxygen consumption had first been increased by lowering its environmental temperature, the same degree of hypoxia caused a sharp fall
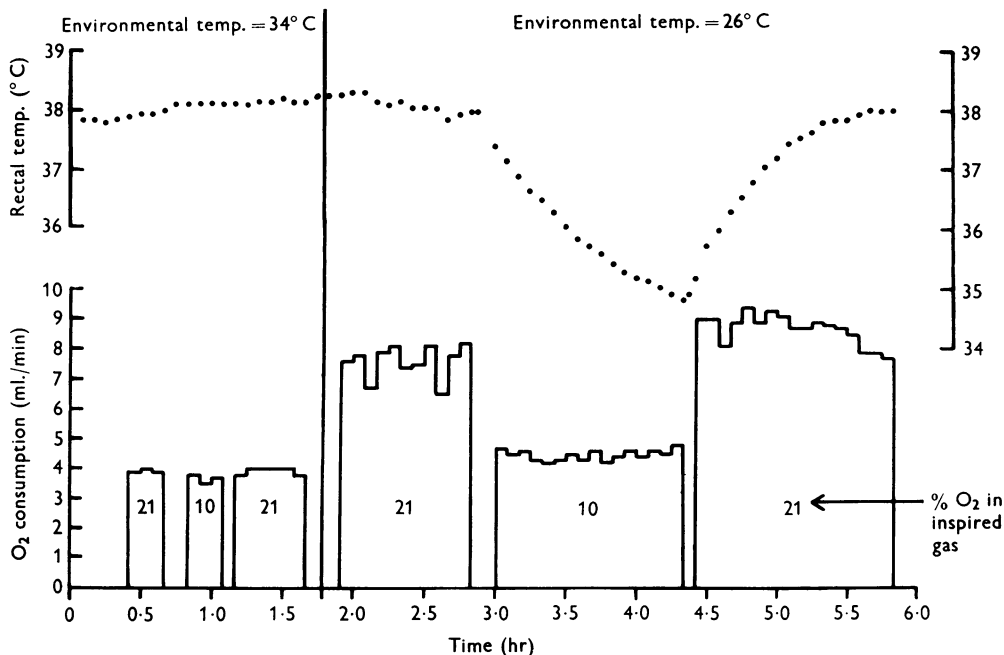

Fig. 5. The plotted results from an experiment in which a kitten, age 15 days, weight 282 g, was subjected to hypoxia (10 % oxygen) at two different controlled environmental temperatures: first at its neutral temperature, 34° C; then at 26° C, which is below the neutral temperature. ......, animal's rectal temperature. The block diagram shows the animal's oxygen consumption (averaged over 5 min periods); the oxygen percentage in the inspired gas is indicated by the numeral inside each block.

in oxygen consumption, and a slower, more or less exponential, fall in rectal temperature. It should be noted that the animal became cyanosed when breathing 10 % oxygen, and the degree of cyanosis appeared to be the same whether the animal was at its neutral temperature or at the lower environmental temperature.

The same general response to 10 % oxygen was also shown by a very much smaller and younger kitten; this is demonstrated in Fig. 6. This type of response has been obtained without exception in all kittens older than 24 hr. Thus the

experiment illustrated in Fig. 5 is typical; this figure exemplifies various further points which will now be considered.

Special aspects of the phenomenon at the low environmental temperature. In the latter part of this experiment (Fig. 5), when the animal was below its neutral temperature, hypoxia was maintained for almost an hour and a half. During this time the oxygen consumption remained more or less at the level to which it fell at the onset of the hypoxia, while over the same period the animal's rectal temperature fell from about 38·0 to 34·8° C. The sudden fall in oxygen consumption was thus a primary response to hypoxia, while the gradual fall in rectal temperature was a secondary effect consequent upon the reduction in
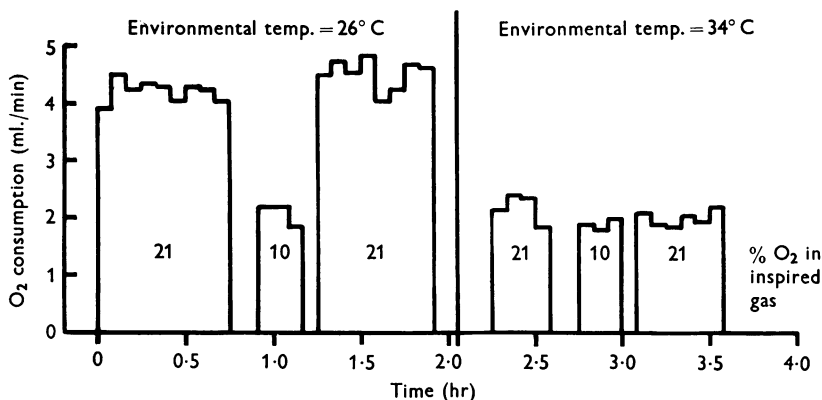

Fig. 6. Results from an experiment of a similar nature to that shown in Fig. 5; but in this case the kitten was very much younger, 2 days old, weight 124 g. Conventions as for Fig. 5.

metabolism (von Flückiger, 1956; Moore, 1956). This difference in time course disposes of the argument, mentioned by Gellhorn (1943), that the decrease in metabolism is a *result* of the fall in body temperature (through a Q_{10} effect). In fact, in spite of the fall in body temperature, no further fall in oxygen consumption was observed throughout the period of hypoxia.

While at the lower environmental temperature the animal was not obviously more active when breathing 21% oxygen than when breathing 10% oxygen; in fact, the reverse was the case. The depression in oxygen consumption produced by 10% oxygen was, therefore, not just due to a reduction in gross activity. Neither was it due to the reduction in shivering shown by Hemingway & Birzis (1956), since the animal never shivered, even when it was breathing 21% oxygen.

One further point should be mentioned. The slight restraint imposed by the snug fit of the animal in the chamber is not sufficient to cause the phenomenon of restraint hypothermia (see e.g. Wilber & Robinson, 1958), so this is not a complicating factor.

Is an oxygen debt paid back after hypoxia? The activity of the animal is not

shown in Fig. 5, but it was noted that the animal was conspicuously agitated when it was hypoxic. Activity of this degree would have led to a definite increase in oxygen consumption had it occurred while the animal was breathing 21 % oxygen; yet there was no increase in oxygen consumption during hypoxia. The source of energy for this increased muscular activity is thus something of a mystery. If an oxygen debt was incurred, there is no sign, at the neutral temperature, that it was paid back when the oxygen concentration was restored to 21 %; and this process could hardly be completed within the 1–2 min occupied by the change over from 10 to 21 % oxygen. It is true that, at the *low* environmental temperature, immediately the oxygen concentration was restored to 21 % the animal's oxygen consumption rose to levels that are significantly higher ($P < 0.001$ in Fig. 5) than during the control period. At the same time, however, the animal's rectal temperature started to rise, in a roughly exponential fashion, towards the control value; and it was *only* while the rectal temperature was rising that the animal's oxygen consumption was significantly greater than during the control period (Fig. 5 clearly illustrates this). As the rectal temperature neared its former value of about 38° C the oxygen consumption fell off, and regained its control level at roughly the same time as the rectal temperature ceased to rise. In the experiment illustrated, the total extra oxygen consumed amounted to approximately 95 ml. This would yield between 450 and 480 cal. Taking a value of 0.83 for the specific heat of the body (Burton & Edholm, 1955, pp. 41–42), approximately 750 cal would be required to heat the whole animal through the observed 3.2° C. However, at the 26° C environmental temperature a heat gradient is maintained between the rectum and skin, so less heat will actually be required: if two-thirds of the body were heated through 3.2° C, then 500 cal would be needed. Though this calculation can hardly be more than an approximation, it shows that thermal changes alone can easily account for all the extra oxygen consumed. Thus it cannot be maintained that an oxygen debt has been paid back, only that a heat debt has been paid back (see also Fig. 8, adult guinea-pig).

The composite picture. By repeating the type of experiment shown in Figs. 5 and 6 at various oxygen levels and various environmental temperatures a more complete picture is obtained. The results are shown in Fig. 7 where oxygen consumption (ml./min. kg$^{2/3}$, ordinates) has been plotted against the oxygen percentage in the inspired gas (abscissae) at various environmental temperatures (represented by the different symbols).

Since the amount of extra metabolism evoked by a cold environment depends on the animal's thermal insulation, any particular environmental temperature will not evoke the same increase in oxygen consumption in animals of all ages and sizes. For this reason, each symbol does not represent a unique environmental temperature. Instead, the environmental temperature has been chosen for each animal to correspond to a given increase in metabolism

in terms of the basal metabolic rate. Each symbol therefore corresponds to a range of environmental temperatures, not to a single temperature, thus:

    ● = B.M.R. (neutral temperature zone, 34–36° C)

    ◉ ≏ 1·3 × B.M.R. (28–30° C)

    ◖ ≏ 1·7 × B.M.R. (26–28° C)
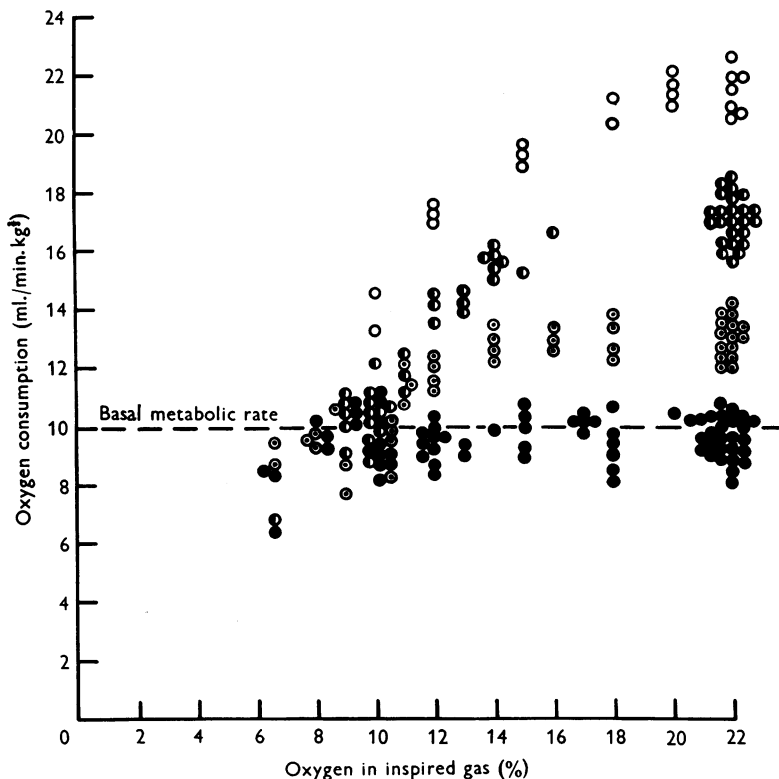
    ○ ≏ 2·1 × B.M.R. (22° C).

Fig. 7. The effect of hypoxia on the oxygen consumption of kittens aged 1–26 days at various controlled environmental temperatures: results obtained from a large number of experiments of the type shown in Figs. 5 and 6. The different symbols denote the various controlled environmental temperatures at which the experiments were performed (see text for further details). Where the points would otherwise have fallen on top of one another, they have been spread slightly in a horizontal direction. Note that kittens below the age of 4 days are not represented at the 22° C environmental temperature.

Figure 7 shows that the oxygen consumption of kittens in a thermally neutral environment did not fall when the oxygen content of the gas they were breathing was reduced, but remained at the basal level until the oxygen concentration had fallen below 10%. In sharp contrast, when the kittens' metabolism had been previously raised, by lowering the environmental temperature, their oxygen consumption was reduced by moderate hypoxia,

and the greater the *extra* oxygen consumption, the more readily was it reduced. Kittens of various ages from 24 hr old onwards are represented in this figure; they all responded similarly. Kittens more than about 10 days old seemed to be slightly better at maintaining their oxygen consumption in the face of hypoxia than were younger kittens; however, the difference was not great.
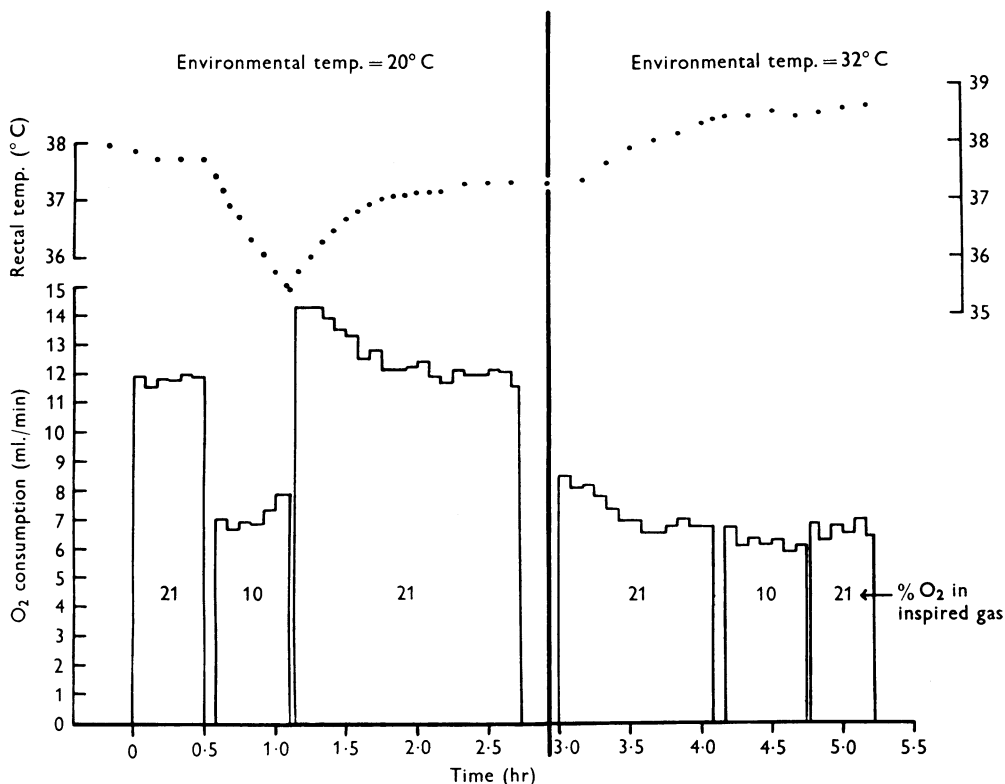

Fig. 8. Results from an experiment in which an adult guinea-pig, weight 500 g, breathed 10% oxygen at two different controlled environmental temperatures, first at 20° C, then at its neutral temperature, 32° C (compare with Fig. 5, kitten). ......, rectal temperature. The block diagram shows oxygen consumption (averaged over 5 min periods); the numeral inside each block indicates the percentage oxygen in the inspired gas.

Kittens less than 24 *hr old*. It will be appreciated that from each litter of kittens only one can possibly be studied within 24 hr of birth. Three such immature animals, which did show a metabolic response to cold, appeared to respond to hypoxia in qualitatively the same manner as the older kittens; but without further experiments one cannot be sure how far the similarity goes. One kitten less than 24 hr old, which failed to show a metabolic response to cold, failed to show a reduction in oxygen consumption in response to breathing 10% oxygen when it was at a low environmental temperature.

Adult guinea-pigs

The response to hypoxia shown by adult guinea-pigs follows essentially the same pattern as that just described for kittens (compare Figs. 8 and 9 with Figs. 5, 6 and 7); further detailed description seems unnecessary. However, the environmental temperature required to evoke, say, a doubling of the basal metabolic rate is lower in guinea-pigs than in kittens because of the somewhat greater thermal insulation of the former.
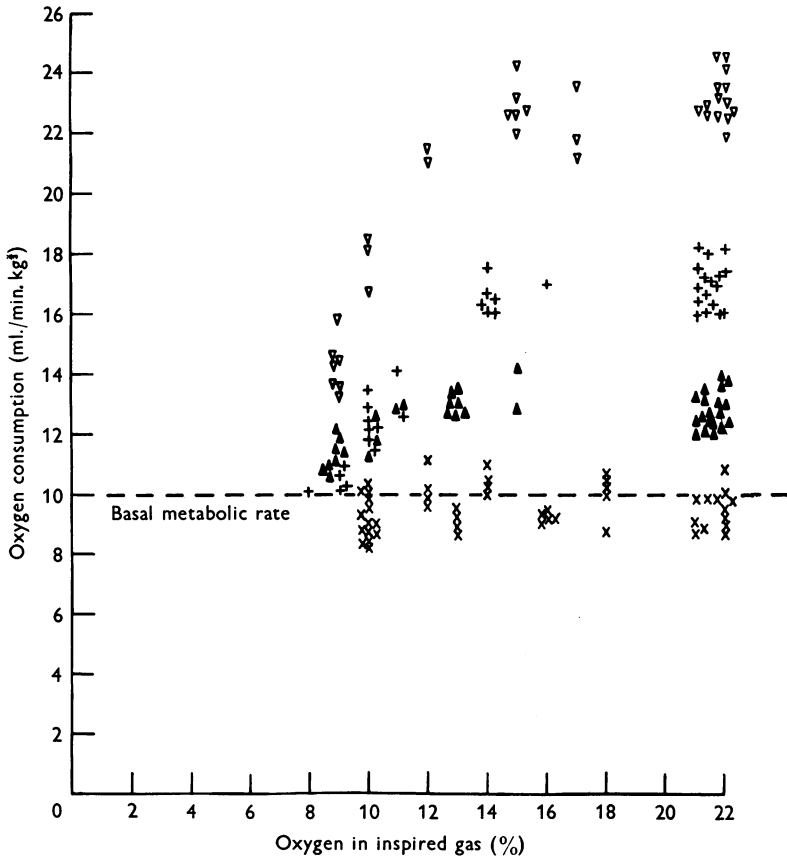

Fig. 9. The effect of hypoxia on the oxygen consumption of adult guinea-pigs at various controlled environmental temperatures (compare with Fig. 7, kittens). The different symbols denote the various environmental temperatures at which the experiments were performed: ▽ 10–15° C, + 20–25° C, ▲ 26–30° C, × 32° C (neutral temperature).

The conclusion reached as a result of the experiments shown in Fig. 3 is confirmed; namely, that reduction in oxygen consumption as a result of hypoxia is not a response shown by new-born animals only. In all cases the type of response obtained is determined largely by the level of metabolism

immediately before the induction of hypoxia; and the level of metabolism at rest is in turn determined by the environmental temperature to which the animal is exposed.

<div align="center">DISCUSSION</div>

It will have been noted that oxygen consumption measurements have been used as the sole guide to the rate of metabolism, and no determinations of CO_2 production have been made; in fact, throughout this paper oxygen consumption, metabolism and heat production have been used interchangeably as though they were proportional to one another. This is more or less true when the animal is breathing 21 % oxygen, but does not necessarily apply when it is hypoxic—for here metabolism (i.e. chemical reaction) may proceed anaerobically, as well as aerobically. Incidentally, the heat evolved during the performance of a given amount of work when the energy is obtained anaerobically, by glycolysis for example, is much less than when the energy is obtained by aerobic processes (approximately half in the case of muscular work, see, for instance, A. V. Hill, 1928). Nevertheless, the rate of metabolism cannot be *less* than is indicated by the oxygen consumption.

CO_2 production was not measured because in this investigation metabolism was studied during transitory states. Under these circumstances CO_2 output will have no significance, since it will give no hint of the metabolic processes that are actually occurring. There are very considerable stores of CO_2 in the body, and the exact amount stored varies, depending particularly on the pulmonary ventilation (Farhi & Rahn, 1955): it is only during the steady state that an animal's CO_2 output accurately represents its metabolic CO_2 production. During hypoxia there are even more uncertainties in the interpretation of CO_2 production, since anaerobic and aerobic processes may both be going on at the same time.

Oxygen, on the other hand, cannot be stored in the body to any great extent; consequently, over any given period the animal's oxygen absorption faithfully represents the oxygen utilized in the body—and incidentally the steady state is achieved very rapidly after altering the oxygen tension in the inspired gas. The uncertainty in interpreting CO_2 output is thus very much greater than the error in calculating metabolism (less than $\pm 3\%$) that could arise solely from disregarding variations in the respiratory quotient.

The results presented here indicate that kittens and adult guinea-pigs both respond in a similar way to hypoxia of moderate severity. Moreover, in response to a given degree of hypoxia, oxygen consumption may be either unchanged, or greatly decreased, depending entirely on whether the animal was originally consuming oxygen at its basal rate or faster than this. In these experiments the animal's original metabolic rate was varied by varying the environmental temperature. These results must now be considered in relation to previous reports about the effects of hypoxia in adult and new-born animals.

The relevant literature is rather confusing. Oxygen consumption, as we have seen, depends on many factors; and, unfortunately, published reports do not always contain sufficient experimental detail to allow a proper assessment. This makes it difficult to compare one set of results with another. In addition one has to distinguish carefully between acute and chronic hypoxia, because there is no doubt that acclimatization greatly increases tolerance to hypoxia, and considerably modifies the response. Also, two different methods are used to produce hypoxic hypoxia—by lowering the ambient barometric pressure, or by reducing the proportion of oxygen present. These have customarily been compared on the basis of the partial pressure of oxygen in the atmosphere, but it seems more reasonable to compare the gases after saturation with water at body temperature; so this procedure has been followed here, employing the formula

$$O_2\% \text{ at 1 atm} \equiv \frac{(p-47) \times 20 \cdot 96}{760-47}.$$

where p is atmospheric pressure (mm Hg). For further discussion, see Fenn, Rahn & Otis (1946).

Acheson *et al.* (1957), McCance & Widdowson (1957) and Cross *et al.* (1958) have recently discussed various aspects of the literature concerned with the effect of hypoxia on man and animals, both adult and new-born. Therefore only a brief summary of the essential findings will be given here, starting with adult man and going on to smaller adult mammals, then to infant and new-born animals.

Adult man. Almost all the experimental work on hypoxia in man seems to have been done either at high altitudes, or in a decompression chamber. It appears to be dangerous for an unacclimatized man to breathe an atmosphere containing oxygen at a tension much less than 75 mm Hg (19,000 ft. (5793 m) ≏ 9% oxygen at 1 atmosphere) for even a short length of time (Matthews, 1954), and unacclimatized men have died from breathing an atmosphere, with an oxygen tension of about 55 mm Hg (27,000 ft. (8230 m) ≏ 6·2% oxygen)—for example, Sivel and Croce-Spinelli. Huckabee (1958) mentions that fasting, resting human subjects given 10% oxygen to breathe showed no decrease in oxygen uptake (acute experiments). In acclimatized man under basal or near-basal conditions oxygen consumption is unchanged between sea-level and 22,000 ft. (6706 m) ≏ 8% oxygen (Houston & Riley, 1947; Pugh, 1957). Nevertheless, even at lower altitudes than this there is a considerable reduction in maximal work output and maximum oxygen consumption (Dill, Edwards, Fölling, Oberg, Pappenheimer & Talbott, 1931; Henderson, 1939; Pugh, 1958).

Adult smaller mammals. In adult dogs at rest death occurs at below 6% oxygen (acute exposure), but oxygen consumption does not fall until death is imminent (Cordier & Mayer, 1935; Gorlin & Lewis, 1954; Huckabee, 1958).

With still smaller mammals one finds apparently conflicting reports. In rabbits, for example, Ogata (1923) showed that oxygen consumption fell progressively with increasing hypoxia below 14%; on the other hand, Hamon, Kolodny & Mayer (1935) found that the oxygen content of the inspired air could be reduced down to 8–4% without a fall in oxygen consumption. Rats given 10% oxygen showed a 30% decrease in oxygen uptake (von Flückiger, 1956); Blood, Elliott & D'Amour (1946) found about the same decrease as the barometric pressure was lowered from 5000 ft. to 32,000 ft. (1524 m to 9752 m) i.e. down to the equivalent of 4·7% oxygen at 1 atm, but since they were working at Denver, Colorado, their rats were acclimatized to 5000 ft. Lintzel (1931) subjected rats to low pressure at different environmental temperatures; they showed a marked fall in oxygen consumption at ordinary temperatures, but a slight increase at high temperatures. Mice show a decrease in oxygen consumption in proportion as the oxygen content of the gas they breathe is decreased below 20% (Chevillard & Mayer, 1935). In this and other evidence, the over-all impression given is that the larger mammals show no reduction in oxygen consumption with hypoxia but that the smaller mammals are more sensitive.

New-born mammals. The new-born appear to behave like adult small mammals. The oxygen consumption of human new-born infants (Cross *et al.* 1955, 1958) and of puppies and kittens (Moore, 1956 *a*, *b*) is reduced when they are given 15% oxygen or less to breathe instead of air. Cross and his associates have also shown, by a type of direct calorimetry, that the heat production of the human infant is lower when breathing 15% oxygen than when breathing air (Brodie, Cross & Lomer, 1956, 1957). Finally, Acheson *et al.* (1957) showed a reduction in the oxygen consumption of foetal and new-born lambs when their arterial oxygen saturation fell below 35%.

The experimental results described in this paper are compatible with all these reports. They reveal, in addition, that whether or not there is a reduction in oxygen consumption in response to moderate hypoxia depends largely on the environmental temperature.

*Hypothesis to explain the apparent difference between small
and large mammals*

Obviously it is desirable to see whether an explanation can be found that will fit, and unify, the various findings that have been discussed above. It seems to me that the apparent difference between large and small animals, and the conflicting reports about small animals, could all be explained by the fact that whether or not moderate hypoxia causes a reduction in an animal's oxygen consumption depends largely on whether the animal was originally metabolizing at its basal rate, or faster than this.

At ordinary ambient temperatures the resting metabolic rate (per $kg^{2/3}$) of

smaller animals tends to be higher than that of larger animals; this arises simply from the fact that a small animal usually has a thinner pelt and less insulation than a larger one. This fact has two consequences for the small animal: its neutral temperature is high; and its metabolism rises more steeply as the environmental temperature falls below the critical value. (Of course, this does not apply equally to all small mammals: those which live in cold regions usually possess a pelt of good insulating properties, for example the arctic ground squirrel (Erikson, 1956) and the arctic lemming (Scholander, Hock, Walters, Johnson & Irving, 1950).) Rats, mice and guinea-pigs are all well below their critical temperature under ordinary experimental conditions at room environmental temperatures (Herrington, 1940), whereas dogs (Rubner, 1902) and clothed men (Winslow, Herrington & Gagge, 1937; Erikson, Krog, Andersen & Scholander, 1956) are not. This would account for the difference between the effects of hypoxia on large and small mammals; and in a thorough search of the literature I have not been able to find experimental evidence that contradicts this view. Indeed, where it is possible to make a reasonable judgement as to the original metabolic rate, the evidence actively supports this explanation.

The same considerations must apply when new-born animals are compared with more mature ones. Both the new-born and adult animals studied here reacted to environmental temperature and to hypoxia in a qualitatively similar manner. The quantitative differences can be explained in terms of differences in thermal insulation and maximal oxygen absorbing power; but the phenomenon appears to be essentially the same in both cases. Nevertheless, it is well known that foetal and new-born animals can survive anoxia better than adults.

Factors concerned in the ability of the new-born to survive anoxia

In none of the experiments reported here was hypoxia taken to such an extreme degree as to kill the animal, and it was not the purpose of these experiments to discover the degree of hypoxia that the animals could survive. However, a large number of factors are concerned in the greater ability of the new-born animal to survive anoxia; environmental temperature and body temperature are two of them. It is interesting to speculate whether, at a neutral temperature (where body temperature can fall to only a very limited extent), an oxygen tension so low that basal oxygen demands cannot be satisfied is compatible with survival for longer than a few minutes. As far as adult animals are concerned, the available evidence suggests that (at a presumably normal body temperature) a fall below basal oxygen consumption is rapidly followed by circulatory failure and the death of the animal (see, for example, Cordier & Mayer, 1935; Gorlin & Lewis, 1954). At low environmental temperatures, on the other hand, the body temperature *is* free to fall, and does

so as a result of hypoxia. Experiments with adult small mammals (Phillips, Saxon & Quimby, 1950; Gray, 1955) and with infant animals (Edwards, 1824; Fazekas, Alexander & Himwich, 1941; Adolph, 1948; Miller & Miller, 1954) show that, until the low body temperature itself proves lethal, the lower the body temperature the longer the survival time without oxygen. This probably reflects a 'Q_{10} effect', that is, the lower the body temperature the smaller the oxygen requirement. In this respect new-born animals seem to have the advantage, since they survive cooling to a lower body temperature than do adults (Adolph, 1948, 1951).

In warm-blooded animals the 'Q_{10} effect' may be obscured by the metabolic response to cold. However, under circumstances where the metabolic response to cold is abolished, the rapidity with which the body temperature falls will depend on (1) the difference between the temperature of the animal and the environment; (2) the animal's size; and (3) the animal's thermal insulation; a fall being favoured by a large thermal gradient, a small size and a small thermal insulation. My observations (unpublished) indicate that the thermal insulation of a kitten is small at birth, but increases rather rapidly with age. Therefore, at a given low environmental temperature, a new-born animal (being favoured on the last two counts) will cool more rapidly than an older animal or adult of the same species. Compared with an adult of the same *size*, the new-born will be favoured on the last score; thus the new-born are better suited to withstand anoxia. The magnitude of the metabolic response to cold must also affect the issue. Preliminary observations of my own suggest that new-born animals which are able to show such a response probably have a smaller maximal metabolic increase than do adults. There is plenty of evidence that biochemical and localized metabolic factors are also concerned (see, for example, Himwich, Bernstein, Herrlich, Chesler & Fazekas, 1942; Himwich, Fazekas & Homburger, 1943; Hicks, 1953; Dawes, Mott & Shelley, 1958, 1959); but further investigation, paying strict attention to the *physical* variables enumerated above will be necessary in order to decide to what degree *they* contribute to the greater resistance of the new-born to anoxia.

The 'extra' metabolism that is depressed by hypoxia

It has been shown experimentally in the preceding sections that the extra metabolism provoked by a cold environment is especially sensitive to hypoxia. Two questions inevitably come to mind: first, what is the site of this extra metabolism, and second, is an increase in metabolism arising from other causes equally sensitive to hypoxia?

Heat is produced easily and conveniently by muscular activity, but there has been much debate over whether the whole of the increased output of heat that occurs in response to cold comes from the activity of striated muscle (see Burton & Edholm, 1955, pp. 148–157, for a discussion on this subject).

Shivering is a well known muscular activity that is evoked by cold environments. However, large increases in metabolism have been observed in the absence of visible shivering (Lusk, 1928; and my own observations). Where does the extra heat come from in this case? Though it may be generated by 'thermal muscular tone' (Burton & Bronk, 1937), there is recent evidence that even when the striated muscles have been completely paralysed with curare animals are still able to show a marked metabolic response to cold (Cottle & Carlson, 1956). Thus the question is still not settled. Nevertheless, it should always be borne in mind that the mere absence of visible shivering does not necessarily mean that the animal is at its neutral temperature, neither does it imply that the metabolic rate is basal.

It does not seem likely that the extra metabolism evoked by cold is specifically and uniquely depressed by hypoxia; it is much more probable that at low oxygen tensions metabolism in general is limited by the animal's ability to absorb oxygen from the atmosphere and transport it to the tissues that need it. If this is true, one would expect the extra metabolism of exercise to be limited in a similar manner at low oxygen tensions. On this point I could find no direct experimental evidence that was strictly applicable to acute hypoxia. There is, however, evidence concerning acclimatized man at high altitudes. Henderson (1939) emphasized that 'at every altitude, the amount (of oxygen that a man can consume) is limited by the barometer'. He thought that a man's maximum oxygen consumption would be reduced to about the basal level at the summit of Everest—at an atmospheric oxygen tension of approximately 50 mm Hg (29,000 ft. $\simeq$ 5·5 % oxygen at 1 atm). Pugh's (1958) Fig. 8 shows a striking decline in maximum oxygen consumption with increasing altitude. Extrapolation suggests that maximum oxygen consumption is reduced to the basal level at an atmospheric oxygen tension of around 45 mm Hg tension (31,000 ft. (9450 m) $\simeq$ 5 % O_2 at 1 atm). Pugh's results were obtained in athletic, fit and very well acclimatized men: probably *unacclimatized* men are reduced to their basal metabolic level at a somewhat higher atmospheric oxygen tension, say 60 mm Hg (25,000 ft. (7720 m) $\simeq$ 7·0 % oxygen at 1 atm), instead of 45 mm Hg. At this altitude an unacclimatized man becomes unconscious within 5–7 min, and sooner than this if he is performing a task (Stewart, 1954).

Activity during hypoxia and its source of energy

In my experiments the animals showed, in 10 % oxygen, a certain amount of muscular activity that was not accompanied by a significant increase in oxygen consumption. There are two possible explanations for this. First, it may be that the movements observed, though they appeared to be vigorous, actually represented only a very small performance of mechanical work, and thus demanded only a slight increase in oxygen consumption. Certainly in man one of the most striking subjective effects of acute hypoxia is the marked

muscular weakness and impaired capacity for doing physical work that it produces (Haldane, Kellas & Kennaway, 1919). Since the animal's movements were not being made against a resistance, this weakness would hardly show itself. The second possibility is that an appreciable amount of energy was being expended, but that it was obtained anaerobically by glycolysis, with the production of lactic acid. In my experiments there was no evidence that an 'oxygen debt' was paid back after a period of hypoxia, showing that lactate was not immediately built back into glycogen. This fact does not rule out the second possibility, since lactate might be retained, and slowly used up in the ordinary processes of metabolism (perhaps by the heart, which is well known to be able to oxidize lactate directly).

The practical significance of the findings

By the experiments and arguments put forward in this paper I have tried to show that the *level of metabolism* determines the effect of hypoxia on oxygen consumption in large and small mammals, adults and new-born alike. Can this knowledge be put to use?

In practice our chief concern is with human infants, and these studies were intended to throw some light (indirectly) on the plight of the hypoxic baby. The evidence of Cross *et al.* (1958) suggests that babies react to hypoxia in much the same way as do kittens and other mammals—at least if it can be presumed that in their experiments the babies were below their neutral temperature. Preliminary experiments of my own (unpublished observations) indicate that premature infants react to a slightly lowered environmental temperature by increasing their oxygen consumption in the same way as other mammals. However, it has recently become the practice to maintain incubators at a lower temperature than was previously thought desirable (29° C instead of 35° C; Franklin, 1959), in the hope that the lowered body temperature that results will in turn mean a diminished demand for oxygen. The first requirement for managing the situation is an awareness of the factors that are operating. Assuming that the treatment of the hypoxic baby should be aimed at reducing its metabolic requirements to a minimum, there appear to be two quite distinct ways of doing this: either (1) by keeping the infant at its neutral environmental temperature, or (2) by keeping the infant in a cold environment, thus reducing its body temperature, so that the 'Q_{10} effect' can operate. It looks as though it is essential to decide at the outset which of these courses to follow in any particular case, since an in-between course would appear to give the worst of both worlds. Method (2) seems attractive; but at present there is no experimental evidence as to its effectiveness in reducing the baby's metabolic requirements, and there is always the possibility of cold injury. In this connexion, it has long been known that, under comparably cold conditions, frost-bite occurs more frequently at high altitudes: this could indicate

that the general reduction in metabolism due to hypoxia combines with local (circulatory) hypoxia to accelerate the fall in tissue temperature, thus increasing the chance of cold injury. Here is an additional reason for circumspection in using method (2) for the frankly hypoxic baby.

Giaja & Andjus (1949) and Andjus & Smith (1955) have used hypoxia in combination with a low environmental temperature as a method of inducing hypothermia in small mammals; the experiments described here show the rational basis for this procedure, and indicate how it should be controlled. The deprivation of oxygen should never be such as to reduce oxygen consumption below the 'basal' level corresponding to the body temperature at each moment, otherwise anoxic injury can be expected. In clinical practice hypoxia is not used to facilitate the production of hypothermia; instead, drugs (such as chlorpromazine) are used. It is not as yet known whether these drugs act on metabolism in a manner similar to hypoxia.

In conclusion, there now seems little justification for the perpetuation of Van Liere's sweeping and widely quoted statement 'it is now generally believed that gaseous metabolism is independent of variations in barometric pressures' (Van Liere, 1942, p. 196). This statement has been interpreted very literally (which may not have been his intention, since he himself pointed out some exceptions), and has for that reason given rise to some misconceptions. It should certainly not be applied without qualification, paying due attention both to the degree of 'variation in barometric pressure' and to the initial level of metabolism; the latter, in turn, will depend on the environmental temperature and the animal's thermal insulation, as well as on its muscular activity.

SUMMARY

1. It has been reported that new-born animals reduce their oxygen consumption in response to hypoxia, whereas adults do not. In order to discover whether it is size or maturity that determines the response, this phenomenon has been investigated in kittens (aged 1–40 days) and in adult guinea-pigs of roughly the same size.

2. A closed-circuit apparatus is described which measures the rate of oxygen consumption of an unanaesthetized single small mammal accurately with good time resolution ($\Delta t = \frac{1}{2}$–1 min), while the environmental temperature and oxygen content of the inspired gas are both held constant at any desired level. Alteration of the two latter parameters is accomplished easily and rapidly.

3. A fall in oxygen consumption in response to moderate hypoxia (15–10 % oxygen) was shown by both kittens and adult guinea-pigs; therefore this type of response is not characteristic of new-born animals. However, whether or not it appears *does* depend on the environmental temperature.

4. At a neutral environmental temperature (i.e. when the metabolic rate is basal) oxygen consumption is unaffected by reducing the oxygen content of

the inspired air down to 10%. In contrast, when the environmental temperature has been lowered (so that, when breathing 21% oxygen, the animal has increased its metabolic rate in order to maintain its body temperature) the oxygen consumption does fall when hypoxia is induced; and the greater the *extra* oxygen consumption the more readily is it reduced. Both kittens and adult guinea-pigs respond in a qualitatively similar manner.

5. During hypoxia, at a neutral temperature the animal's rectal temperature does not fall, but at a lower environmental temperature the rectal temperature does fall (this is a consequence of the reduction in oxygen consumption). The 'heat debt' that accumulates during hypoxia is paid back promptly when the oxygen content of the inspired air is restored to 21%.

6. Whatever the environmental temperature, if an 'oxygen debt' is incurred during hypoxia (down to 10% oxygen), there is no evidence that it is paid back on restoring the oxygen to 21%.

7. The findings outlined in (3) and (4) above are discussed in relation to previous reports on the effect of hypoxia in adult and new-born animals. The conflicting results previously reported for small mammals, and the apparent difference between them and larger mammals, can both be explained by the hypothesis that hypoxia leads to lowered oxygen consumption only if the metabolic rate was originally above the basal level.

8. Various physical and physiological factors which influence metabolic rate are discussed, and also factors concerned in the ability of the new-born to survive anoxia.

9. The practical significance of these findings is considered, particularly with reference to the hypoxic new-born baby.

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